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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
KC/B45196		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/09368	22/09/2000	24/09/1999
International Patent Classification (IPC) or national classification and IPC A61K9/00		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/04/2001	22.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hauss, R Telephone No. +49 89 2399 8056

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09368

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-27 as originally filed

Claims, No.:

1-36 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 33-35.

because:

   ☒ the said international application, or the said claims Nos. 33-35 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 13, 15-32, 36

	No:	Claims	1-12, 14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32, 36
Industrial applicability (IA)	Yes:	Claims	1-32, 36
	No:	Claims	

2. Citations and explanations
see separate sheet

R Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 33-35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT, viz., methods of therapeutic treatment of a mammal. Consequently, no opinion unter Article 33(1) PCT will be given with respect to novelty, inventive activity and the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

   For the assessment of present claims 33-35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:

   D1: WO-A-96 36352 D2: WO-A-99 52549

3. Document D1 discloses liquid pharmaceutical agent formulations for oral or nasal delivery comprising at least two absorption enhancers. The absorption enhancers are selected from a group of compounds comprising, i.a., polyoxyethylene x-lauryl ether wherein x is 9-20, p-t-octyl phenoxy polyoxyethylene, polyoxyethylene ether, polyoxyethylene sorbitan esters and monoolein (D1: cl. 1). Deoxycholate, sodium deoxycholate, chenodeoxycholate, taurodeoxycholate and glycochenodeoxycholate are also included in the list of suitable absorption enhancers (D1: cl. 1). The adjuvant combination according to D1 provides effective and practical oral or nasal delivery of pharmaceutical agents (D1: p. 2, l. 36 - p. 3, l. 1).

   In a preferred embodiment one of the enhancing compounds is polyoxyethylene x-lauryl ether wherein x is 9 or 10 (p. 4, ll. 23-24).

In further preferred embodiments (D1: cl. 3) the following combinations of absorption enhancing compounds are used:

- a combination of sodium deoxycholate, chenodeoxycholate, polyoxyethylene 9-lauryl ether and monoolein,

- a combination of deoxycholate, chenodeoxycholate, taurodeoxycholate, polyoxyethylene 9-lauryl ether and monoolein,

the concentration of each of the compounds in the pharmaceutical formulation being from 1% to 5% (wt/wt) and especially from 1.5% to 3.5% (wt/wt) (D1: cl. 2).

In example V of D1, a combination comprising monoolein, deoxycholate and polyoxyethylene 9-lauryl ether is disclosed.

The combination of absorption enhancers according to D1 can be used in pharmaceutical formulations comprising various types of pharmaceutical agents, such as viral and bacterial antigens, cholera toxin B-subunit, interleukin and cytokins (D1: cl. 11).

3.1 Based on the embodiment disclosed in D1 (p. 4, ll. 23-24), wherein one of the enhancing compounds is polyoxyethylene x-lauryl ether with x = 9 or 10, only one selection from the list of compounds as defined in present claim 1 is required in order to arrive at an adjuvant combination comprising a polyoxyethylene alkyl ether of formula (I) and an additional non-ionic surfactant. Thus, the subject-matter of claims 1-3, 5-8 and 10-12 is not novel in view of the cited embodiment.

Furthermore, the embodiments disclosed in claim 3 and example V of D1 are prejudicial to the novelty of present claims 1, 4-12 and 14.

Thus, the present application does not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 1-12 and 14 is not new in the sense of Article 33(2) PCT over the disclosure of D1.

3.2 The present application furthermore does not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 13, 15-32 and 36 does not involve an inventive step in the sense of Article 33(3) PCT.

The problem to be solved by the present invention may be regarded as providing a novel adjuvant system for a medicament, in particular for a vaccine.

As discussed above, the adjuvant combination as disclosed in present claim 1, as well as several of its embodiments as disclosed in claims 2-12 and 14, are already known from D1. Further embodiments disclosed in dependent claims 13, 16-18 and independent claim 15 concern modifications falling within the normal practice of the skilled person and/or furthermore encompassed by the teaching of D1. Thus, the subject-matter disclosed in said claims would be accessible to the skilled person without the exercise of inventive skill.

The addition of agents which are known to enhance immunological responses is disclosed in claim 11 of D1. Hence, the subject-matter of present claims 19-22 does not appear to involve an inventive step.

The formulation of vaccines comprising the presently claimed adjuvant combinations is suggested by claim 11 of D1. Accordingly, the subject-matter of present claims 23-26, 28, 32 and 36 does not involve an inventive activity in the light of D1.

Apart from oral delivery, nasal delivery is also envisaged in D1. Hence, the embodiments defined in present claims 27 and 29-31 are obvious in view of D1.

4. The PCT application WO-A-99 52549 (D2) published on 21.10.1999 was filed on 29.03.1999. The present application claims the priority dates of 24.09.1999 and 06.07.2000. Thus, D2 was published after the first priority date but before the second priority date of the present application.

4.1 Pending availability of the priority documents for the present application, it cannot be decided at the present time for which parts of the application document D2 is to be regarded as state of the art according to Article 33(2)-(3) PCT, pursuant to rule 64.1(a)-(b) and 64.3 PCT.

4.2 D2 discloses vaccine compositions suitable for mucosal application comprising an antigen, an excipient, and a polyoxyethylene ether or ester (D2: cl. 1). Preferably, the polyoxyethylene ether or ester is a surfactant of formula (I): $HO(CH_2CH_2O)_n$-A-R (D2: cl. 2), wherein n, A and R are defined as in present claim 1. The compositions may optionally comprise an additional immunostimulant (D2: cl. 14-16; p. 7, l. 5 - p. 8, l. 15). In one embodiment, the polyoxyethylene ethers or esters may be admixed with glycerol monoesters, i.e., an additional non-ionic surfactant (D2: cl. 17; p. 8, l. 17-21). Thus, the disclosure of D2 differs from the presently claimed subject-matter in that the presence of an additional non-ionic surfactant is not mandatory. However, this feature is envisaged in claim 17 of D2 and would also

appear obvious in the light of D1.

4.3 If the first priority date of the present application were found not to be valid, D2 would have to be regarded as state of the art according to Article 33(2)-(3) PCT for all parts of the application. In this case, the subject-matter claimed in the present application would be regarded as lacking inventive activity over D2 (Article 33(3) PCT, for the reasons stated above.